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Brivaracetam as add-on treatment in patients with post-stroke epilepsy: real-world data from the BRIVAracetam add-on First Italian netwoRk Study (BRIVAFIRST)

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ABSTRACT

Objective: Post-stroke epilepsy (PSE) is one of the most common causes of acquired epilepsy and accounts for about 10-15% of all newly diagnosed epilepsy cases. However, evidence about the clinical profile of antiseizure medications in the PSE setting is currently limited. Brivaracetam (BRV) is a rationally developed compound characterized by high-affinity binding to synaptic vesicle protein 2A. The aim of this study was to assess the 12-month effectiveness and tolerability of adjunctive BRV in patients with PSE treated in a real-world setting.
Methods: This was a subgroup analysis of patients with PSE included in the BRIVAracetam add-on First Italian netwoRk Study (BRIVAFIRST). The BRIVAFIRST was a 12-month retrospective, multicentre study including adult patients prescribed adjunctive BRV. Effectiveness outcomes included the rates of seizure response (≥50% reduction in baseline seizure frequency), seizure-freedom, and treatment discontinuation. Safety and tolerability outcomes included the rate of treatment discontinuation due to adverse events (AEs) and the incidence of AEs.

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Results: Patients with PSE included in the BRIVAFIRST were 75 and had a median age of 57 (interquartile range, 42-66) years. The median daily doses of BRV at 3, 6, and 12 months from starting treatment were 100 (100-150) mg, 125 (100-200) mg and 100 (100-200) mg, respectively. At 12 months, 32 (42.7%) patients had a reduction in their baseline seizure frequency by at least 50%, and the seizure freedom rates was 26/75 (34.7%). During the 1-year study period, 10 (13.3%) patients discontinued BRV. The reasons of treatment withdrawal were insufficient efficacy in 6 (8.0%) patients and poor tolerability in 4 (5.3%) patients. Adverse events were reported by 13 (20.3%) patients and were rated as mild in 84.6% and moderate in 15.4% of cases.
Significance: Adjunctive BRV was efficacious and generally well-tolerated when used in patients with PSE in clinical practice. Adjunctive BRV can be a suitable therapeutic option for patients with PSE.

1. Introduction

Stroke is a leading disease worldwide, with an estimated incidence of more than 15 million cases annually [1]. Post-stroke epilepsy (PSE), which is defined as the occurrence of one or more unprovoked epileptic seizures at least one week after the stroke, develops in at least 4-6% of the stroke population [2]. Cerebrovascular disease is one of the most common causes of acquired epilepsy and accounts for about 10-15% of all newly diagnosed epilepsy cases [2]. Although PSE has overall a good prognosis and patients are generally responsive to pharmacological treatment, approximately 20% of the patients are pharmaco-resistant [3, 4]. Risk factors of difficult to control seizures include the younger age at stroke onset, haemorrhagic stroke subtype, stroke severity and occurrence of status epilepticus as the first late-onset epileptic symptom [5].

Currently, evidence about the clinical profile of antiseizure medications (ASMs) in the setting of PSE is limited. Brivaracetam (BRV) is a rationally developed compound with a high-affinity binding to synaptic vesicle protein 2A (SV2A) and one of the most recently approved ASMs. Brivaracetam is licensed in Europe as adjunctive therapy of focal seizures in patients ≥4 years of age with epilepsy, and in the United States as both monotherapy and adjunctive therapy for the treatment of focal seizures in patients ≥1 month of age.

The BRIVAFIRST (BRIVAracetam add-on First Italian netwoRk STudy) investigated the use of adjunctive BRV in everyday clinical practice over a 1-year period [6]. With more than 1,000 patients included, the BRIVAFIRST represents the largest real-world BRV study conducted so far, and the size of the cohort allows for sub-analyses to be performed. The aim of this analysis was to evaluate the effectiveness and tolerability of adjunctive BRV in patients with PSE who were included in the BRIVAFIRST.

2. Methods

2.1. Participants

The BRIVAFIRST was a retrospective study performed at 62 Italian centers [6]. Adult patients attending participating centers who were prescribed to BRV (March 2018-March 2020) and were on stable treatment with ≥1 ASM during the prior 90 days were retrospectively identified. In Italy, BRV required the therapeutic plan on template of the Italian Medicine Agency to be prescribed and reimbursed by the National Health Service as adjunctive treatment in patients aged 16 years or older with focal seizures who have not responded to prior, appropriately chosen and used ASM schedules. Exclusion criteria were history of alcoholism, drug abuse, conversion disorders or other non-epileptic ictal events. Among participants with focal epilepsy and 12-month follow-up after initiating BRV, patients with PSE were considered in the current analysis. Post-stroke epilepsy was defined as the occurrence of one or more unprovoked seizures at least one week after ischemic or haemorrhagic stroke. Data on demographics, clinical history, type of seizures and epilepsy [7], etiology, previous/concomitant ASMs, baseline seizure frequency (monthly seizure frequency during the 3 months before starting BRV) were collected. Data on seizure occurrence, adverse events (AEs), and drug withdrawal were retrieved from patient seizures diaries and clinical records; visits at 3, 6, and 12 months were performed as standard practice when a new ASM is initiated.

Effectiveness outcomes included the rates of seizure response (≥50% reduction in baseline monthly seizure frequency), seizure-freedom, seizure worsening (>25% increase in monthly seizure frequency relative to baseline) and treatment discontinuation at 12 months. Further analyses were performed using data obtained from the visits at 3- and 6 months. Seizure-freedom at each time point was defined as the occurrence of no seizures since at least the previous visit: at 12 months, it was considered as no seizures during the preceding 6 months, and at 3 and 6 months was defined as lack of seizures since baseline or the 3-month visit, respectively. Safety and tolerability outcomes included the rate of treatment discontinuation due to AEs and the incidence of AEs considered BRV-related by participating physicians.

2.2. Statistical analysis

Values were presented as median (interquartile range) for continuous variables and number (percent) of subjects for categorical variables. Comparisons were made using the Mann-Whitney test or Chi-squared test, as appropriate. Results were considered significant for p values <0.05 (two sided). Data analysis was performed using STATA/IC 13.1 (StataCorp LP, TX, USA). The study is reported according to STROBE guidelines [8].

2.3. Standard protocol approval

This study was approved by the Ethical Committee at all participating sites and was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from any patient and/or their parent or legal representative.

3. Results

Out of 1,325 patients initially identified within the BRIVAFIRST, 71 patients were excluded as diagnosed with generalized, combined, or unknown epilepsy and 225 because follow-up after initiating BRV was less than 1 year at time of the current analysis. Among 1,029 participants with focal epilepsy who fulfilled the inclusion/exclusion criteria, 75 (7.3%) had PSE and were considered in this analysis. The median age of the patients was 57 (42-66) years, and 36 (48.0%) were men. Baseline characteristics of patients are summarized in Table 1. According to levetiracetam (LEV) status, 23 (30.7%) patients were LEV naïve and 52 (69.3%) patients had history of LEV use. Patients with history of LEV treatment had a higher number of lifetime ASMs in comparison to LEV naïve patients (p=0.002) (Table 2).

The median daily dose of BRV at 3 months was 100 (100-150) mg; it was 125 (100-200) mg at 6 months, and it was 100 (100-200) mg at 12 months. The reduction in baseline seizure frequency was ≥50% in 27 [36.0%, 95% confidence interval (CI) 95% CI 25.8-47.7%] patients at 3 months, 31 (41.3%, 95% CI 30.6-53.0%) patients at 6 months, and 32 [42.7%, 95% confidence interval (CI) 31.8-54.3%] patients at 12 months from starting BRV. Seizure freedom was achieved by 18 (24.0%, 95% CI 15.5-35.2%) patients at 3 months, 24 (32.0%, 95% CI 22.3-

Table 1
Baseline characteristics of patients

Characteristics	Patients with post-stroke epilepsy (n=75)
Age, years	57 (42-66)
Male sex	36 (48.0)
Age at epilepsy onset, years	41 (19-57)
Duration of epilepsy, years	10 (4-21)
Type of seizure ([a]N=68)	
Focal onset	48 (70.6)
Focal to bilateral tonic-clonic	15 (22.1)
Focal onset and focal to bilateral tonic-clonic	5 (7.4)
Number of previous ASMs ([a]N=74)	4 (2-6)
Levetiracetam status	
Never used	23 (30.7)
Prior use/prescribed at baseline	52 (69.3)
Number of concomitant ASMs	1 (1-2)
[b]Baseline monthly seizure frequency	4 (1-10)

Data are median (IQR) for continuous variables, and n (%) for categorical variables. [a]N refers to the total number of patients for whom data in question were available.
[b]Based on the number of seizures during the 90 days before starting adjunctive-BRV.
Abbreviations: ASM=anti-seizure medication; IQR=interquartile range.

Table 2
Baseline characteristics of patients according to levetiracetam status

Characteristics	Levetiracetam naïve (n=23)	Levetiracetam prior (n=52)	p
value			
Age, years	59 (38-67)	56 (42-64)	0.483
Male sex	13 (56.5)	23 (44.2)	0.326
Age at epilepsy onset, years			0.389
Median	47 (21-59)	35 (19-54)	
Duration of epilepsy, years			0.301
Median	8 (3-18)	12 (4-23)	
Type of seizure			0.685
[a]N	22	46	
Focal onset	14 (63.6)	34 (73.9)	
Focal to bilateral tonic-clonic	6 (27.3)	9 (19.6)	
Focal onset and focal to bilateral tonic-clonic	2 (9.1)	3 (6.5)	
Number of previous ASMs			0.002
[a]N	23	51	
Median	2 (1-4)	4 (2-7)	
Number of concomitant ASMs	1 (1-2)	2 (1-2)	0.290
[b]Baseline monthly seizure frequency	4 (2-6)	4 (1-15)	0.601

Data are median (IQR) for continuous variables, and n (%) for categorical variables. [a]N refers to the total number of patients for whom data in question were available.
[b]Based on the number of seizures during the 90 days before starting adjunctive-BRV.
Abbreviations: ASM=anti-seizure medication; IQR=interquartile range.

43.6%) patients at 6 months, and 26 (34.7%, 95% CI 24.6-46.3%) patients at 12 months. The rates of seizure response and seizure freedom during the follow-up are shown in Fig. 1. The rates of seizure worsening were at 8.0% (95% CI 3.6-17.0%), 6.7% (95% CI 2.7-15.3%), and 1.3% (95% CI 0.2-9.2%) at 3-, 6-, and 12-month follow-up visits.

According to LEV status, there was no difference in the responder rate at 3 months between LEV naïve patients and patients with history of LEV (LEV naïve: 43.5%, 95% CI 24.0-65.2%; LEV prior: 32.7%, 95% CI 21.1-46.9%; p=0.370); the responder rates at 6 months (LEV naïve: 60.9%, 95% CI 38.6-79.4%; LEV prior: 32.7%, 95% CI 21.1-46.9%; p=0.022) and 12 months (LEV naïve: 69.6%, 95% CI 46.6-85.7%; LEV prior: 30.8%, 95% CI 19.5-45.0%; p=0.002) were significantly higher among LEV naïve patients compared to LEV prior patients. There were no statistically significant differences in the rates of seizure freedom at 3 months (LEV naïve: 13.0%, 95% CI 3.9-35.8%; LEV prior: 28.8%, 95% CI 17.9-43.0%; p=0.140), 6 months (LEV naïve: 34.8%, 95% CI 17.4-57.4%; LEV prior: 30.8%, 95% CI 19.5-45.0%; p=0.731), and 12 months (LEV naïve: 43.5%, 95% CI 24.0-65.2%; LEV prior: 30.8%, 95% CI 19.5-45.0%; p=0.286) between patients who were LEV naïve versus patients who had prior LEV use.

During the 1-year study period, 10 (13.3%, 95% CI 7.2-23.3%) patients discontinued BRV. The reasons of treatment withdrawal were insufficient efficacy [n=6 (8.0%, 95% CI 3.6-17.0%)] and AEs [n=4 (5.3%, (95% CI 2.0-13.6%)]. Adverse events were reported by 13 (20.3%, 95% CI 12.0-32.3%) patients and were rated as mild in 84.6% (95% CI 49.0-96.9%) and moderate in 15.4% (95% CI 3.1-51.0%) of the cases. The AEs observed are summarized in the Table 3.

4. Discussion

This exploratory *post hoc* analysis of BRIVAFIRST data indicated that BRV was effective in improving seizure control and generally well tolerated when used as add-on treatment under clinical practice conditions in patients with PSE.

So far, other evidence for the use of BRV in patients with PSE is very limited. In the BRIVA-LIFE study, the 12-month seizure freedom rate was 40.9% among the 22 patients who had experienced a stroke and was significantly greater than the rate of 17.5% observed in patients without PSE [9].

In the cohort of patients with PSE who were included in the BRIVAFIRST, adjunctive BRV reduced baseline seizure frequency both in LEV naïve and LEV prior patients, suggesting that a history of LEV treatment does not preclude the prescription of BRV. Differences in responder rates also indicated a greater improvement in seizure control among patients with no LEV history than in patients with prior exposure to LEV. Patients with historical LEV use had a significantly higher

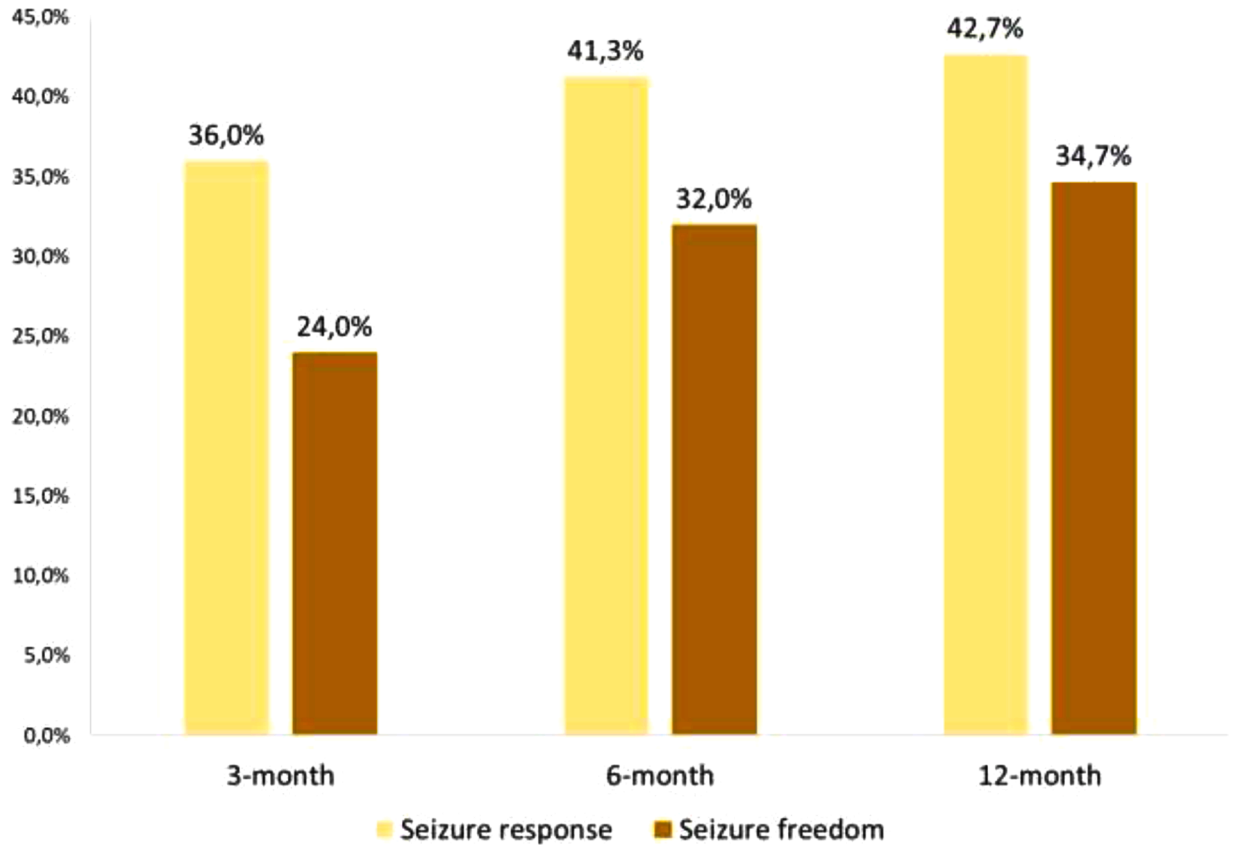

Fig. 1. Clinical response to adjunctive brivaracetam.
Rates of seizure response and seizure freedom at 3, 6 and 12 months are reported. Seizure response was defined as a reduction in seizure frequency of ≥50% in comparison to baseline seizure frequency.

Table 3
Adverse events with brivaracetam treatment

Patients with adverse events	
[a]N	64
n (%)	13 (20.3)
***Reported adverse events**	
[a]N	64
Anxiety	2 (3.1)
Headache, n (%)	2 (3.1)
Nervousness and/or agitation, n (%)	2 (3.1)
Aggressiveness, n (%)	1 (1.6)
Constipation, n (%)	1 (1.6)
Dizziness, n (%)	1 (1.6)
Fatigue, n (%)	1 (1.6)
Memory disturbance, n (%)	1 (1.6)
Mood change, n (%)	1 (1.6)
Sleep disturbances, n (%)	1 (1.6)
Somnolence, n (%)	1 (1.6)
Vertigo, n (%)	1 (1.6)

[a] N refers to the total number of patients for whom data in question were available.

number of lifetime ASMs than patients never exposed to LEV, and this feature may be an indicator of intrinsic epilepsy severity and more difficult-to-treat seizures [10,11]. Similar results have been already observed. In a real-world, time-based analysis, the median time-to-baseline seizure count after BRV initiation was longer for LEV naïve than LEV prior patients, and patients who had received LEV had a higher number of prior and concomitant ASMs and a higher baseline seizure frequency compared to patients that had never been treated with LEV [12]. In a pooled analysis of data from randomized, controlled trials, previous treatment failure with commonly prescribed ASMs, including LEV, carbamazepine, lamotrigine, and topiramate was associated with a reduced response to BRV irrespective of the mechanism of action, and patients with previous exposure to any of the considered drugs had a higher number of prior ASMs than patients who had never been exposed [13].

The tolerability and safety of adjunctive BRV were good in patients with PSE. This favourable profile appears clinically relevant in this population, which is often characterized by advanced age and frailty and is more sensitive to adverse effects [14]. Additional considerations for treatment of patients with PSE include the frequent coexistence of

comorbidities, like hypertension, cardiac disease, atrial fibrillation, and dyslipidaemia, and comedications [15]. In this regard, the low potential of BRV to induce or inhibit the cytochrome system and the unlikely effect on the efflux of substrates mediated by the P-glycoprotein result in a low risk of relevant drug-drug interactions, including those with oral anticoagulants and digoxin [16].

BRIVAFIRST is the largest cohort of patients treated with BRV according to routine clinical practice to be reported so far, and the number of patients with PSE included in this subgroup analysis outweighed the evidence from other real-world data [9]. The study was performed under the usual circumstances of healthcare practice rather than rigid protocols and the results are characterized by high external validity and generalizability. Several limitations need, however, to be considered. The open-label design and retrospective nature may have introduced potential confounders and a less ambitious clinical care of elderly may have affected the discontinuation rate observed in the study. The unavailability of information about stroke type, stroke aetiology, concomitant medical conditions and pharmacological treatment apart from epilepsy did not allow exploring any influence of these variables on the efficacy and tolerability of BRV treatment. The lack of data about serum levels of BRV and concomitant drugs prevented us from exploring the individual interactions between medications. The collection of AEs based on the records of clinical visits rather than standardized questionnaires might have resulted in underreporting. Further, the lack of a control group of matching patients assigned to receive an alternative treatment did not allow to draw any conclusion about the comparative efficacy of BRV versus other ASMs.

The evidence supporting the use of specific ASMs in patients with PSE is limited. Only few trials have been designed to specifically assessed or compared ASMs in patients with unprovoked post-stroke seizures, and patients with epilepsy of cerebrovascular aetiology are typically under-represented in regulatory trials [17–19]. Accordingly, data from real-world practice can become a useful complement to guide the therapeutic approach. Among patients with PSE included in BRIVAFIRST, adjunctive BRV was associated with the improvement in seizure control, good tolerability, and no safety concern. These data suggest that BRV can be a suitable option in this specific, generally more vulnerable population. Further studies including larger cohorts of patients are warranted to build upon this preliminary evidence and provide additional information and guidance for clinical decisions.

Declaration of Competing Interest

Simona Lattanzi has received speaker's or consultancy fees from Angelini, Eisai, GW Pharmaceuticals, and UCB Pharma, and has served on advisory boards for Angelini, Arvelle Therapeutics, Bial, EISAI, and GW Pharmaceuticals. Laura Canafoglia has received consultancy fee from Eisai. Maria Paola Canevini has received speaker's or consultancy fees from Bial, Eisai, Italfarmaco, Sanofi, and UCB Pharma. Sara Casciato has participated in pharmaceutical industry-sponsored symposia for Eisai, UCB Pharma and Lusofarmaco. Valentina Chiesa has received speaker's or consultancy fees from Eisai and UCB Pharma. Edoardo Ferlazzo has received speaker's or consultancy fees from Angelini, Arvelle Therapeutics, Eisai, GW Pharmaceuticals, and UCB Pharma. Angela La Neve has received speaker's or consultancy fees from Angelini, Arvelle Therapeutics, Bial, Eisai, GW Pharmaceuticals, Mylan, Sanofi, and UCB Pharma. Patrizia Pulitano has received consulting fees or speaker honoraria from UCB Pharma and Eisai. Federica Ranzato has received speaker's fees from Eisai, UCB, and Livanova. Eleonora Rosati has received fees for participation in advisory board or scientific consultation from Eisai, GW Pharmaceuticals, Bial, and UCB Pharma. Laura Tassi has received speaker's or consultancy fees from Arvelle Therapeutics, Eisai and UCB Pharma. Carlo Di Bonaventura has received consulting fees or speaker honoraria from UCB Pharma, Eisai, GW Pharmaceuticals, Bial, and Lusopharma. Emanuele Cerulli Irelli, Filippo Dainese, Giovanni De Maria, Giuseppe Didato, Giancarlo Di Gennaro, Giovanni Falcicchio, Martina Fanella, Massimo Gangitano, Oriano Mecarelli, Elisa Montalenti, Alessandra Morano, Federico Piazza and Chiara Pizzanelli have no conflicts of interest to declare.

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APPENDIX: BRIVAFIRST Group Membership

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